Clinical genomics and cancer immunotherapy

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Disclosures

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• Equity
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Outline

• State of “immunogenomic” clinical biomarkers
• Bridging clinical and functional cancer immunogenomics for discovery
• Casting a wider net to study all tumors in the immunotherapy era
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Current state of genomics and cancer immunotherapy

Tumor mutational burden

CTLA4 Ab and melanoma

CTLA4 Ab and melanoma

PD-1 Ab and NSCLC

PD-1 Ab and MSI-high tumors

Snyder et al. *NEJM* 2014
Rizvi et al. *Science* 2015
Le et al. *NEJM* 2015
Neoantigens are generated from tumor-specific mutations, and may be especially good targets for the anti-tumor immune response because they are:

1) specific to the tumor and
2) foreign to the immune system
Is TMB sufficient?

New findings in @NEJM are shedding light on using TMB vs PD-L1 as an immunotherapy biomarker. More on our blog: bit.ly/2vcsydG

Van Allen, Miao, Schilling et al Science 2015
Is TMB sufficient?

Hellmann MD et al, *Cancer Cell*, 2018
n = 75, NSCLC patients treated with ipi + nivo (CheckMate-012)

Miao, Margolis, Vokes et al
*Nature Gen* 2018, n = 249
Clinical genomics and response to immune checkpoint blockade

• Mutational load/neoantigens
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A patient living with metastatic kidney cancer

Life expectancy: 0-3 months

Can tumor genomics impact immunotherapy response in kidney cancer?

Five years later...

December 2017
Genomic mediators of response to cancer immunotherapy?

Lawrence et al, Nature 2013
Mutational load and clear cell renal cell carcinoma

Best response | Response group
--- | ---
CR | Clinical benefit (n=11)
PR | Intermediate benefit (n=11)
SD | No clinical benefit (n=13)
PD | 

![Graph showing the relationship between mutational load and clinical benefit.](image)

Response
- Clinical benefit (n=11)
- Intermediate benefit (n=11)
- No clinical benefit (n=13)

Miao et al. Science 2018
Specific genes involved?

Miao et al. Science 2018
Clinical and experimental validation?

RCC validation cohort
PBRM1 p < 0.01

Gao et al *PNAS* 2017 (Kaelin Lab)
Miao et al *Science* 2018
A role for SWI/SNF in cancer immunotherapy?
Linking clinical genomics to functional and transcriptional findings

Pan, et al Science 2018

Canadas et al Nature Med 2018
A role for SWI/SNF in cancer immunotherapy?

Hodges, Kirkland, and Crabtree  Cold Spring Harb Perspect Med 2016
Complex biology of SWI/SNF in cancer

- Numerous interactions suggest complex interplay with other immuno-oncology modifiers
- Additional lineage-specific factors likely at play
- Functional and clinical investigations underway
- **Not a clinical biomarker!**

Hodges, Kirkland, and Crabtree *Cold Spring Harb Perspect Med* 2016
McDermott et al *Nature Medicine* 2018
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Expanding functional screens and cancer immunotherapy

In vivo CRISPR screening identifies Ptpn2 as a cancer immunotherapy target

Identification of essential genes for cancer immunotherapy

Identification of CMTM6 and CMTM4 as PD-L1 protein regulators

A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing

CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity

Tumor immune evasion arises through loss of TNF sensitivity
Expanding clinical cohorts to match functional findings

WES on tumor samples from patients receiving immune checkpoint therapy (n = 314)

Exclusions (n = 65):
- Clinical benefit unclear
- Tumor-in-normal contamination (≥1%)
- Tumor sample contamination (≥5%)
- Low tumor purity (<10%)
- Low normal mean target coverage (<15×)
- Low tumor mean target coverage (<25×)
- Failed sequencing realignment

n = 249 tumors in final analysis

- Melanoma (n = 151)
- Lung cancer (n = 57)
- Bladder cancer (n = 27)
- HNSCC (n = 12)
- Other (n = 1 sarcoma, n = 1 anal cancer)

Opportunities to connect clinical and functional genomics across cancer types

Diana Miao
Claire Margolis
Natalie Vokes
Linking genomics with outcomes remains major barrier to discovery

Miao, Margolis, Vokes et al. Nature Genetics 2018
Cell cycle and cancer immunotherapy?

CDK4/6 inhibition triggers anti-tumour immunity

Cyclin D–CDK4 kinase destabilizes PD-L1 via Cul3SPOP to control cancer immune surveillance

Research Articles

CDK4/6 Inhibition Augments Anti-Tumor Immunity by Enhancing T Cell Activation

DOI: 10.1158/2159-8290.CD-17-0918

Miao, Margolis, Vokes et al Nature Genetics 2018
PI3K/PTEN and cancer immunotherapy resistance?

Peng et al Cancer Discovery 2015
Miao et al Immunity 2017
Placing single-gene correlates in broader molecular contexts

**PIK3CA**

- p.E542K
- p.E545K
- p.E726K
- p.R88Q
- p.C420R
- p.H1047R
- p.E600K
- p.V344G
- p.S323F
- p.R916C
- p.E418K
- p.D454H
- p.V711

**Proportion of mutations from APOBEC signature**

Miao, Margolis, Vokes et al *Nature Genetics* 2018
Placing single-gene correlates in broader molecular contexts

Miao, Margolis, Vokes et al. Nature Genetics 2018
Power to detect single gene correlates of response is still limited due to sample size.
DFCI/Broad Center for Cancer Precision Medicine: Capturing tumor, immune, and stromal programs

Pre-treatment biopsy+blood
- Bulk WES/WTS
- scRNASeq
- Models
- Liquid WES

On-therapy biopsy+blood
- Bulk WTS
- scRNASeq
- Liquid WES

Resistance biopsy+blood
- Bulk WES/WTS
- scRNASeq
- Models
- Liquid WES

Standard of care anti-PD1
CCPM Biopsy Program

Bruce Johnson, Asaf Rotem, many others
Direct to patient studies for access to standard of care samples?

You can have a direct impact on the future of men with prostate cancer

The Metastatic Prostate Cancer Project is a nationwide genomic research study for men with advanced or metastatic prostate cancer. We seek to generate the most comprehensive database that will be shared with the entire research community to accelerate discoveries.

mpcproject.org
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